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An Efficient PIFA-Mediated Synthesis of a Directly Linked Zinc Chlorin Dimer via Regioselective Oxidative Coupling

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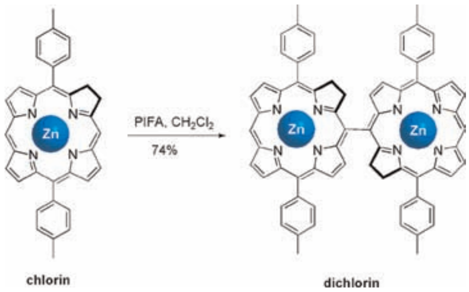
ABSTRACT



The synthesis of a directly linked zinc chlorin dimer was first achieved by a facile and efficient oxidative coupling of zinc chlorin monomers with phenyliodine bis(trifluoroacetate) (PIFA). The reaction shows high regioselectivity at the 20-position near the hydrogenated pyrrole ring producing selective dichlorin in 74% yield.

Porphyrin and chlorin dimers have attracted significant attention due to their numerous applications such as artificial photosynthetic systems, sensors, and nonlinear optical (NLO) devices.[1] In recent years, contributions from several research groups have resulted in the facile synthesis of directly linked porphyrins by oxidative coupling.[2] It has been shown that the short distance and electronic interaction between porphyrin units imparted predominant photophysical properties to the molecules, such as effective energy transfer and low energy absorption bands.[3] Chlorins are structurally more similar to natural photosynthetic pigments than porphyrin.[4] Besides their application as models to understand the key steps of the natural photosynthetic mechanism, many bis-chlorin model structures bridged by ether, ester, and C–C at varied distances have recently been reported[5] as effective photosensitizers for photodynamic therapy (PDT). However, the synthesis of

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(1) For some examples of the leading reports, see: (a) Chou, J.-H.; Kosal, M. E.; Nalwa, H. S.; Rakow, N. A.; Suslick, K. S. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, CA, 2000; Vol. 6, Chapter 41. (b) Schwab, P. F. H.; Levin, M. D.; Michl, J. *Chem. Rev.* **1999**, *99*, 1863. (c) Martin, R. E.; Diederich, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 1351.

(2) For some examples of the leading reports, see: (a) Osuka, A.; Shimidzu, H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 135. (b) Ogawa, T.; Nishimoto, Y.; Yoshida, N.; Ono, N.; Osuka, A. *Chem. Commun.* **1998**, 337. (c) Shi, X.; Amin, S. R.; Liebeskind, L. S. *J. Org. Chem.* **2000**, *65*, 1665. (d) Tsuda, A.; Osuka, A. *Science* **2001**, *293*, 79. (e) Jin, L.-M.; Chen, L.; Yin, J.-J.; Guo, C.-C.; Chen, Q. Y. *Eur. J. Org. Chem.* **2005**, 3994. (f) Sahoo, A. K.; Nakamura, Y.; Aratani, N.; Kim, K. S.; Noh, S. B.; Shinokubo, H.; Kim, D.; Osuka, A. *Org. Lett.* **2006**, *8*, 4141. (g) Nakamura, Y.; Aratani, N.; Shinokubo, H.; Takagi, A.; Kawai, T.; Matsumoto, T.; Yoon, Z. S.; Kim, D. Y.; Ahn, T. K.; Kim, D.; Muranaka, A.; Kobayashi, N.; Osuka, A. *J. Am. Chem. Soc.* **2006**, *128*, 4119 and references cited therein.

(3) For some examples of the leading reports, see: (a) Yoshida, N.; Osuka, A. *Tetrahedron Lett.* **2000**, *41*, 9287. (b) Tsuda, A.; Furuta, H.; Osuka, A. *J. Am. Chem. Soc.* **2001**, *123*, 10304. (c) Kim, D.; Osuka, A. *Acc. Chem. Res.* **2004**, *37*, 735. (d) Nakamura, Y.; Hwang, I.-W.; Aratani, N.; Ahn, T. K.; Ko, D. M.; Takagi, A.; Kawai, T.; Matsumoto, T.; Kim, D.; Osuka, A. *J. Am. Chem. Soc.* **2005**, *127*, 236. (e) Maeda, C.; Kamada, T.; Aratani, N.; Osuka, A. *Coord. Chem. Rev.* **2007**, *251*, 2743.

(4) (a) Kobayashi, M.; Akiyama, M.; Kano, H.; Kise, H. In *Chlorophylls and Bacteriochlorophylls: Biochemistry, Biophysics, Functions and Applications; Advances in Photosynthesis and Respiration*; Grimm, B., Porra, R. J., Rüdiger, W., Scheer, H., Eds.; Springer: Dordrecht, 2006; Vol. 25, pp 79–94.

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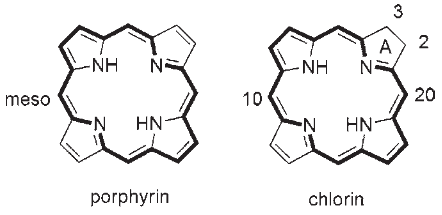
directly linked chlorins via oxidative coupling and the effect of the electronic interaction of the most closely connected units has never been explored.

Scheme 1. Conjugation Pathway of Porphyrin and Chlorin



Recently, hypervalent iodine(III) reagents, such as phenyliodine diacetate (PIDA) and phenyliodine bis(trifluoroacetate) (PIFA), have been widely applied as safe and useful nonmetal oxidants in many organic reactions for their high reactivities and selectivities.[6] The coupling reactions of a metalloporphyrin monomer which has a *meso*-H can be easily and efficiently promoted by hypervalent iodine(III).[2e] This synthesis strategy has also been used, in our group, to achieve the synthesis of chiral diporphyrins and fused diporphyrins.[7] The mechanism for porphyrin to carry out such a reaction was previously widely considered as involving single electron transfer (SET) oxidation. It was thought that the porphyrin radical cation, produced via SET oxidation, coupled itself to form the dimer.[8−10] Compared to porphyrin, chlorin has a similar conjugation path and redox properties; however, one pyrrole ring is reduced to a pyrroline ring (Scheme 1). Therefore, we infer that a similar oxidative coupling reaction of chlorin would be realized if the oxidation of the pyrroline ring could be avoided. In this paper, we report an oxidative coupling method for the synthesis of a directly linked chlorin dimer by treating Zn(II) chlorin with PIFA in 74% yield. This coupling reaction shows high regioselectivity at the *meso*-bridge position 20 in the vicinity of the pyrroline ring over the *meso*-bridge position 10.

Scheme 2. Oxidative Reaction of Metal Chlorins

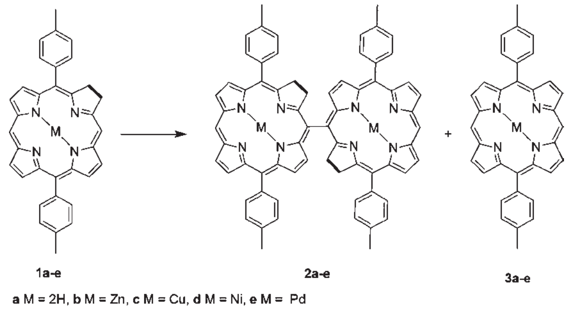


Table 1. Yields of the Oxidative Reaction of Metal Chlorins

		yield/%[a]		
entry	reactant	DDQ[b]	PIDA[c]	PIFA[c]
1	**1a**	80 (**3a**)	N.R.	N.R.
2	**1b**	50 (**3b**)	35 (**2b**)	74 (**2b**)
3	**1c**	48 (**3c**)	N.R.	58 (**3c**)
4	**1d**	30 (**3d**)	N.R.	54 (**3d**)
5	**1e**	78 (**3e**)	N.R.	66 (**3e**)

[a] Isolated yield of **2b** and **3a**−**e**. [b] The amount of added oxidant was 1.0 equiv. [c] The amount of added oxidant was 0.5 equiv.

In our experiments, the metal chlorins, prepared via a streamlined synthesis,[11] were treated with the oxidants DDQ (2,3-dichloro-5,6-dicyanobenzoquinone), PIDA, and PIFA (Scheme 2). The oxidants were added to a solution of **1a**−**e** in CH_2Cl_2 under nitrogen. The directly linked chlorin dimer was only obtained by the reaction of Zn(II) chlorin with hypervalent iodine(III) reagents (Table 1, entry 2). Pd(II), Cu(II), and Ni(II) chlorins were oxidized by PIFA and DDQ to the respective porphyrin (58−66%) and were inert to PIDA. Moveover, the free base chlorin **1a** reacted with DDQ to produce a porphyrin but was inert to hypervalent iodine(III) reagents. With the Zn(II) chlorin **2a** the oxidative coupling reaction with

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(5) (a) Pandey, R. K.; Dougherty, T. J. *Cancer Res.* **1989**, *49*, 2042. (b) Pandey, R. K.; Smith, K. M.; Dougherty, T. J. *J. Med. Chem.* **1990**, *33*, 2032. (c) Jaquinod, L.; Nurco, D. J.; Medforth, C. J.; Pandey, R. K.; Forsyth, T. P.; Olmstead, M. M.; Smith, K. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1013. (d) Jaquinod, L.; Senge, M. O.; Pandey, R. K.; Forsyth, T. P.; Smith, K. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1840. (e) Johnson, C. K.; Dolphin, D. *Tetrahedron Lett.* **1998**, *39*, 4753. (f) Kozyrev, A. N.; Zheng, G.; Shibata, M.; Alderfer, J. L.; Dougherty, T. J.; Pandey, R. K. *Org. Lett.* **1999**, *1*, 1193. (g) Li, G.; Dobhal, M. P.; Graham, A.; Shibata, M.; Zheng, G.; Kozyrev, A.; Pandey, R. K. *J. Org. Chem.* **2003**, *68*, 3762. (h) Konekamp, T.; Ruiz, A.; Duwenhorst, J.; Schmidt, W.; Borrmann, T.; Stohrer, W. D.; Montforts, F. P. *Chem.—Eur. J.* **2007**, *13*, 6595. (i) Tanaka, T.; Nakamura, Y.; Osuka, A. *Chem.—Eur. J.* **2008**, *14*, 204. (j) Nieves-Bernier, E. J.; Diers, J. R.; Taniguchi, M.; Holten, D.; Bocian, D. F.; Lindsey, J. S. *J. Org. Chem.* **2010**, *75*, 3193.

(6) For selective leading reviews, see: (a) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123. (b) Kita, Y.; Takada, T.; Tohma, H. *Pure Appl. Chem.* **1996**, *68*, 627. (c) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (d) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656. (e) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893. (f) Dohi, T.; Kita, Y. *Chem. Commun.* **2009**, 2073.

(7) (a) Ouyang, Q.; Zhu, Y.-Z.; Li, Y.-C.; Wei, H.-B.; Zheng, J.-Y. *J. Org. Chem.* **2009**, *74*, 3164. (b) Ouyang, Q.; Zhu, Y.-Z.; Zhang, C.-H.; Yan, K.-Q.; Li, Y.-C.; Zheng, J.-Y. *Org. Lett.* **2009**, *11*, 5266.

(8) Shen, D.-M.; Liu, C.; Chen, X.-G.; Chen, Q.-Y. *J. Org. Chem.* **2009**, *74*, 206–211.

(9) (a) Ogawa, T.; Nishimoto, Y.; Yoshida, N.; Ono, N.; Osuka, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 176. (b) Kamo, M.; Tsuda, A.; Nakamura, Y.; Aratani, N.; Furukawa, K.; Kato, T.; Osuka, A. *Org. Lett.* **2003**, *5*, 2079. (c) Hiroto, S.; Osuka, A. *J. Org. Chem.* **2005**, *70*, 4054. (d) Sahoo, A. K.; Nakamura, Y.; Aratani, N.; Kim, K. S.; Noh, S. B.; Shinokubo, H.; Kim, D.; Osuka, A. *Org. Lett.* **2006**, *8*, 4141.

(10) (a) Dohi, T.; Morimoto, K.; Kiyono, Y.; Maruyama, A.; Tohma, H.; Kita, Y. *Chem. Commun.* **2005**, 2930. (b) Dohi, T.; Morimoto, K.; Maruyama, A.; Kita, Y. *Org. Lett.* **2006**, *8*, 2007. (c) Dohi, T.; Ito, M.; Iwata, M.; Kita, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 1301. (d) Kar, A.; Mangu, N.; Kaiser, H. M.; Beller, M.; Tse, M. K. *Chem. Commun.* **2008**, 386.

(11) (a) Whitlock, H. W., Jr.; Hanauer, R.; Oester, M. Y.; Bower, B. K. *J. Am. Chem. Soc.* **1969**, *91*, 5. (b) Balem, F.; Yanamala, N.; Klein-Seetharaman, J. *Photochem. Photobiol.* **2009**, *85*, 471.

PIFA progressed very fast, and the raw material completely disappeared within 5 min. We found that addition of 0.5 equiv of PIFA promoted the reaction in high yield of **2b** (74%). This reaction could also be achieved using PIDA; however, the yield is significantly reduced (35%). As expected, this coupling reaction showed high regioselectivity, and the 20−20′ linked dimer was obtained as the only product. Further addition of oxidants led to the formation of a complex mixture, but not the compound formed by coupling in the *meso*-position 10. Furthermore, the Zn(II) chlorin **1b** could not be oxidatively coupled to **2b** using DDQ; instead it underwent oxidative dehydrogenation to the porphyrin **3b** (50%, entry 2). These results indicate that PIDA and PIFA do not oxidize the pyrroline ring but regioselectively react with the 20-position to generate the dimer.

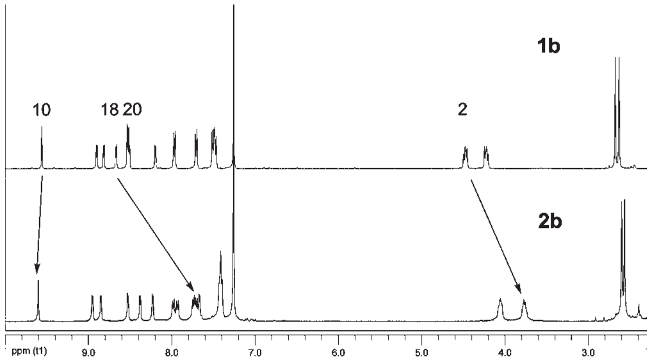

Figure 1. ^{1}H NMR spectra of **1b** and **2b** in $CDCl_3$.

The structure of chlorin dimer **2b** was confirmed by its NMR data and mass spectrometry. The HR-MS of **2b** showed a molecular ion peak at m/z = 1106.273, indicating a dimeric structure. The apperance of a single set of resonances in the NMR spectrum for both chlorin molecules suggested some degree of symmetry of the molecule. A complete ^{1}H NMR assignment for the individual protons of **1b** and **2b** was achieved by 2D-NMR studies. Compared with monomer **1b**, the ^{1}H NMR spectrum of **2b** exhibited a singlet at 9.60 ppm due to H-10 and the signal of H-20 of **1b** disappeared (Figure 1), indicating the two units were joined together at position 20. Additionally, the obvious upfield shifts of the proton signals near the 20-position, especially showing a shifting from 8.69 to 7.68 ppm due to H-18 and from 4.53 to 3.76 ppm due to H-2, further confirmed its dimeric structure with a link at position 20. Additionally, the interaction between H-2 and H-18 can be found in the ^{1}H-NOESY NMR spectrum of **2b** (Supporting Information), which further confirms it links at position 20.

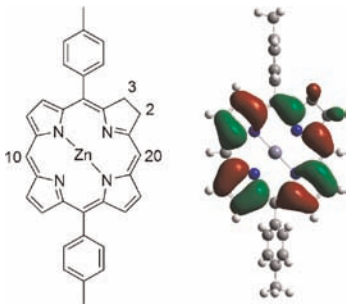

Figure 2. HOMO of Zn(II) Chlorin **1b** derived by calculations at the B3LYP/6-31G(d,p) level, using the LANL2DZ effective core potential for zinc.

The mechanism of the reaction between chlorins and hypervalent iodine(III) may be the same as that for the oxidative coupling of porphyrins. As described, the reactivity of a metal porphyrin should have some relationship with its first oxidation potential.[7b,12] The electrochemical properties of **1a**−**e** and 5,15-diphenyl Zn(II) porphyrin were studied by cyclic voltammetry in CH_2Cl_2 containing 0.1 M tetrabutylammonium hexafluorophosphate (n-Bu_4NPF_6) as a supporting electrolyte. The Zn(II) chlorin **1b** underwent reversible first oxidation at 0.10 V vs Fc/Fc^+, which was quite lower than that of other chlorins (0.21−0.35 V) and 5,15-diphenyl Zn(II) porphyrin (0.37 V). It suggests that Zn(II) chlorin has the highest reactivity and may be easier to oxidize. This explanation was supported by the results of the following experiment: a solution of equivalent amounts of Zn(II) chlorin **1b** and Zn(II) porphyrin **3b** in CH_2Cl_2 was treated with 0.5 equiv of PIFA. The dimer **2b** was formed immediately, but Zn(II) porphyrin **3b** remained unchanged. It implies the regioselective oxidation may result from the high reactivity between Zn(II) chlorin and hypervalent iodine(III) reagents.

Regiocontrolled synthesis of chlorin is an important issue, since chlorin compared to porphyrin has lower symmetry and highly reactive positions.[13] In order to understand this selectivity, a DFT calculation was performed to determine the electron density of **1b**. The energy-minimized structures are calculated with Gaussian 03[14] at the B3LYP/6-31G(d,p) level, using the LANL2DZ[15] effective core potential for zinc. Zn(II) chlorin exhibited the HOMO with electron density at all *meso*-positions and nonreduced β-positions albeit in differing amounts at various positions (Figure 2). The 20-position of chlorin, offering a site for electrophilic reaction,[16] was evaluated to have higher electron density than the other peripheral positions. To confirm the reactivity of the *meso* bridge carbon at the 10 position, the 20-substituted *meso*-triphenyl-2,3-chlorin with the free 10-position, prepared as described,[17] was treated with PIFA under the same conditions. No dimers but several highly polar compounds were

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(12) (a) Felton, R. H.; Linschitz, H. *J. Am. Chem. Soc.* **1966**, *88*, 1113. (b) Fuhrhop, J. H.; Mauzerall, D. *J. Am. Chem. Soc.* **1969**, *91*, 4174.

(13) (a) Liu, C.; Dobhal, M. P.; Ethirajan, M.; Missert, J. R.; Pandey, R. K.; Balasubramanian, S.; Sukumaran, D. K.; Zhang, M.; Kadish, K. M.; Ohkubo, K.; Fukuzumi, S. *J. Am. Chem. Soc.* **2008**, *130*, 14311. (b) Nieves-Bernier, E. J.; Diers, J. R.; Taniguchi, M.; Holten, D.; Bocian, D. F.; Lindsey, J. S. *J. Org. Chem.* **2010**, *75*, 3193. (c) Joshi, P.; Ethirajan, M.; Goswami, L. N.; Srivatsan, A.; Missert, J. R.; Pandey, R. K. *J. Org. Chem.* **2011**, *76*, 8629.

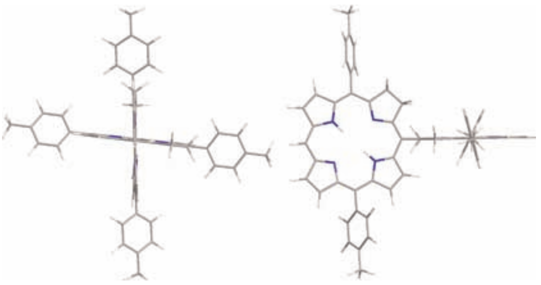

Figure 3. Structure of the directly linked chlorin dimer **2a** as derived by DFT calculations.

observed when excessive oxidant was added. This suggests the chlorins may only be able to couple at the *meso*-position adjacent to the dihydropyrrole ring.

To understand the stereochemical properties of the diaxial systems, the geometry of dimer **2a** was optimized at the B3LYP/3-21G level with no symmetry constraints, using the Gaussian 03 program.[14] For the global minimum structure (Figure 3), the dihedral angle between the chlorin planes in **2a** was found to be 88°. Due to the steric hindrance effect of the dihydropyrrole rings, this angle was smaller than that in *meso*–*meso* directly linked diporphyrin (confirmed to be 90°).[18]

The absorption spectra of zinc(II) chlorin **1b** and directly linked zinc chlorin dimer **2b** are shown in Figure 4. As described, the long-wavelength absorption bands of both compounds have a greatly enhanced oscillator strength at 610 nm. It is worth noting that the *meso*–*meso* directly linked porphyrin dimers always exhibit broadened and split Soret bands because of the exciton coupling between the two perpendicular porphyrin moieties.[18] However, the directly linked zinc chlorin dimer **2b** which had nearly perpendicular aromatic moieties showed two slightly split Soret band at 412 and 418 nm, as well as two remarkablely split Q bands at 617 and 631 nm. Due to their long wavelength absorption in the near-IR region, this type of chlorin could be useful in treating tumors that are deeply seated.

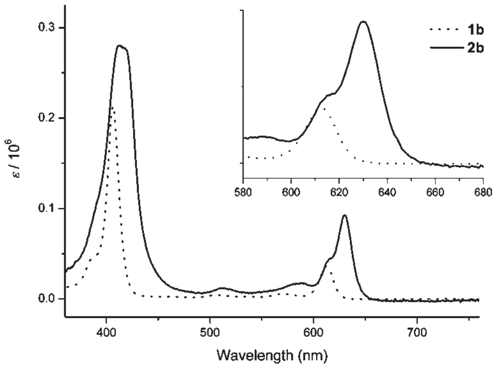

Figure 4. UV–vis spectra of **1b** and **2b** in CH_2Cl_2.

In conclusion, the novel directly linked zinc chlorin dimer was for the first time prepared through a practical and simple oxidative coupling method with a hypervalent iodine(III) reagent. The reaction shows a high degree of regioselectivity at the position near the dihydropyrrole ring to produce the directly linked zinc chlorin dimer linked in positions 20,20′. Further investigations to expand the reaction as well as to develop the photodynamic activities of those novel dichlorins are ongoing and will be reported in due course.

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Supporting Information Available. Experimental procedures and compound data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian03*; Gaussian, Inc.: Wallingford, CT, 2004.

(15) (a) Dunning, T. H., Jr.; Hay, P. J. In *Modern Theoretical Chemistry*; Schaefer, H. F., III, Ed.; Plenum: New York, 1976; Vol. 3, pp 1–28. (b) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 270. (c) Wadt, W. R.; Hay, P. J. *J. Chem. Phys.* **1985**, *82*, 284. (d) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299.

(16) (a) Wray, V.; Jürgens, U.; Brockmann, H., Jr. *Tetrahedron* **1979**, *35*, 2275. (b) Taniguchi, M.; Kim, M. N.; Ra, D.; Lindsey, J. S. *J. Org. Chem.* **2005**, *70*, 275.

(17) Varamo, M.; Loock, B.; Maillard, P.; Grierson, D. S. *Org. Lett.* **2007**, *9*, 4689.

(18) (a) Cho, H. S.; Song, J. K.; Ha, J. H.; Cho, S.; Kim, D.; Yoshida, N.; Osuka, A. *J. Phys. Chem. A* **2003**, *107*, 1897. (b) Cho, S.; Yoon, M. C.; Lim, J. M.; Kim, P.; Aratani, N.; Nakamura, Y.; Ikeda, T.; Osuka, A.; Kim, D. *J. Phys. Chem. B* **2009**, *113*, 10619.

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